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Editorial

Role of Zika Virus in Neural Cell Growth

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"The association between Zika Virus (ZIKV) epidemic and neurological disorder has raised an urgent global alarm. The current epidemic of ZIKV has triggered quick responses in the scientific world. The first case of ZIKV was reported in 2015 from Brazil and now has spread over 30 countries. Nearly four hundred cases of traveler associated ZIKV infection have also been reported in the United States. ZIKV is primarily transmitted by mosquito belongs to the genus *Aedes* that are widely distributed throughout the world. Additionally, the virus can also be transmitted from male to female by sexual contact. The epidemiological investigations during the current outbreak found a causal link between infection in pregnant women and development of microcephaly (MCPH) in their unborn babies. This finding is a cause for grave concern since MCPH is a serious neural developmental disorder that can lead to significant post-natal developmental abnormalities and disabilities. Recently, published data indicates that ZIKV infection severely affects the growth of fetal neural progenitor cells and cerebral neurons resulting into malformation of cerebral cortex leading to MCPH".

Zika virus (ZIKV) outbreak reported for the first time in 2015 from Brazil and has now been spread to over 30 countries. Currently, four hundred cases of ZIKV infection have been reported in United states of America. ZIKV is primarily transmitted by mosquitos of the genus *Aedes* that are widely distributed throughout the world. Additionally, the virus can also be transmitted from male to female by sexual contact [1]. In December 2015, another case report was published confirming the presence of viral particles in the semen of a 44 year old man who had been diagnosed with ZIKV infection two weeks earlier. In February 2016, the center of disease control (CDC) in the USA announced possible sexual transmission in 14 cases, but the mode of transmission was not confirmed. Sexual transmission of Zika virus through infected semen is now well established. The phylogeny of ZIKV suggests two important lineages known as African and Asian, evaluating from one ancestry, mostly apparent in Uganda [3]. Probably the vectors are *Aedes polynesiensis* and *Aedes aegypti*, a species of *Aedes* found in French Polynesia, reported in Yap [4-6]. *Aedes species* found in various parts of USA [2,4]. The viral RNAs has 3419 amino acids and host and viral proteases help in the translation and cleavage of polyprotein into structural and non-structural proteins [7]. Initially, the ZIKV attached with host endosomal membrane by endocytosis and then ssRNA is released into host cytoplasm followed by translation and cleavage of protein and finally resulted in formation of viral proteins. In the next step, the dsRNA produced after replication in endoplasmic reticulum followed by production of additional ssRNAs to form new virus progeny. The newly emerged virus particles move into Golgi complex and finally released into the intracellular spaces to infect the neighboring cells [8]. There is a very close link between flaviviruses such as Zika, Chikungunya and Dengue, which have common symptoms like a headache, rash, myalgia, arthralgia fever, and maculopapular. The published information provided a convincing evidence about the development of neurological symptoms like Dementia in South America and Polynesia [9]. Based on published data the ZIKV infection to pregnant women will lead to the development of MCPH in the developing fetuses [1]. This is a cause for grave concern since MCPH is a serious neural developmental disorder that can lead to serious lifelong developmental abnormalities and disabilities in the affected babies. This disease is characterized by a smaller head circumference with reduced brain size due to a poorly-developed cerebral cortex (Figure 1). The current paradigm is that a key factor in ZIKV-induced MCPH is apoptosis of infected fetal cortical neural stem/progenitor cells those results in depletion of neurons from the cortex and consequent malformation of the cerebral cortex leading to MCPH (Figure 1).

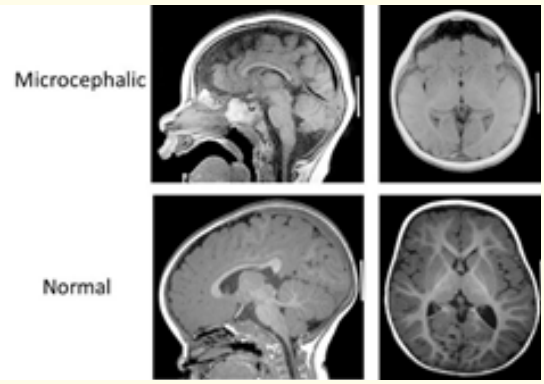

Figure 1: *MRI images from two 10 month old child, the upper one child brain infected with ZIKV with developmental microcephaly and bellow with a head circumference in normal range.*

Neural stem cells damaged by Zika virus

A recently published data has confirmed that ZIKV infection mainly targets on developing human and mouse brain, especially neural progenitor cells with major pathological results. The virus infection in a pregnant mouse could transmit the virus into pups and the abnormal body growth and IUGR in Swiss Jim Lambert mice were observed [10]. ZIKV RNA was detected in many brain tissues of newborn babies [12]. Sincere observation cleared visible cortical abnormalities in the remaining newly born babies with falling number cells, thickness and as well as apparent ocular malformation [12]. Viral infection enabled program cell death in the fetal brain, which changes apoptosis associated gene expressions in a host. The main possibility that why mother–fetal transportation was not detected in C57BL/6 mice was not clear and it is expected that the C57BL/6 mouse may contain a better and strong interferon (I/II IFN) response, or some distinct entry receptor profile as compared to Swiss Jim Lambert mice [12]. Two different research finding, intra peritoneal injection of ZIKV into pregnant mice [11] besides intra cerebral injection into the growing brain [11] also caused in the extended contagion of fetal brain progenitor tissues. Researcher's observed that virus mainly target the embryo radial glial cells [11]. The intra cranially injected virus infection of fetal neural progenitor cells induced cellular apoptosis, and inhibition of neural progenitor cells differentiation [10], which could comprehensibly cause to MCPH. ZIKV is furthermore exhibit to easily infect human neural progenitor cells in culture [10] simultaneously those existing in growing human cerebral organoids [10,12]. These observations resulted in deregulation of neural progenitor cells propagation, differentiation, and induced apoptosis. There are two main pathways where ZIKV infection of the growing fetal brain may impact cortical development. The first one is by the destroying of neural progenitor cells or by deregulating their amount of propagation [12].

Corticogenesis is also affected by ZIKV infection; an especially very important cell type in the fetal brain that is infected by ZIKV is the radial glial cells, which are very the important controller of cerebral cortex improving [12]. ZIKV infection and decay of activity of NPC would axiomatically affect human fetal corticogenesis. Excitingly, AXL is also observed to be produced in the exterior margin of the human neural retina, simultaneously its adjacent marginal area, which could be potentially proof the occurrence of macular atrophy reported viruses-linked microcephalus baby.

ZIKV epidemic in human has been reported with many complications. While this shows up neuronal abnormalities and habit to infect neural progenitor cells, it may also infect the brain cells and affect adult neuronal cells exhibit brain disorder. The neurological symptoms have been identified in ZIKV infection of mice deficient of type I and type II interferon response [12]. The detection of viral particle in the cerebrospinal fluid has been recently observed in an adult then accountable that virus infections that may induce in across the board

systemic infection and viremia in immune-compromised human, may culminate in cerebrospinal fluid infection. This has been reported that TLR-3 is also particularly elevated in ZIKV infection, this is repeatedly accountable that demising of the blood-brain barrier lead to malformation in neuronal cells and tissue in adult.

Conclusion

We have provided an updated information demonstrating the link between ZIKV epidemic and MCPH. Based on the published information provided, it is well known that placental infection of the progenitor neuronal cells in the growing embryo, mainly in the first trimester, is the main primary region for the ZIKV infection linked neuronal malformation. ZIKV efficiently infects human fetus brain cells and tissue both *in vitro* as well as *in vivo*. Animal and mouse models have also repeated critical attitude of human viral pathology related to fetus demise, fetus neuroids epidemiology and cortical growth *in vivo*. This is apparent that the macular degeneration identified with few cases of the microcephalic newly born babies along with a result of ZIKV infection in the growing fetal retinal construction, as it was also observed in virus affected mice, newborn babies. ZIKV deregulate Akt host cell signaling pathway which is very essential for brain development in adult human as well as the fetus. There is few evidence has been reported for the capability of ZIKV to target central nervous system of adult human and induced neuropathy.

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